Unusual formation of tetrahydropyridazine-3,4,5,6-tetracarboxylic and pyrroletetracarboxylic esters upon decomposition of methyl diazoacetate in the presence of pyridine*

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Thermal, photolytic, and thermocatalytic decomposition of methyl diazoacetate (MDA) in the presence of $Rh_2(OAc)_4$ or $Cu(acac)_2$ in refluxing pyridine afforded isomeric *trans*,*cis*- and *cis*,*trans*-3,4,5,6-tetra(methoxycarbonyl)-1,4,5,6-tetrahydropyridazines (~1 : 1) in a total yield of 30—70%. Decomposition of MDA in refluxing *o*-xylene in the presence of $Rh_2(OAc)_4$ and pyridine (20 mol.%) gave rise to 2,3,4,5-tetra(methoxycarbonyl)pyrrole in a yield of up to 40%. In these transformations of MDA, neither dimethyl fumarate (or dimethyl maleate) nor the corresponding 2-pyrazolines were generated as intermediates.

Key words: methyl diazoacetate, tetrahydropyridazines, tetra(methoxycarbonyl)pyrrole, catalysis, thermolysis, photolysis, dediazotization, X-ray diffraction analysis.

Due to high reactivity of derivatives of diazoacetic acid and the presence of several reaction centers in their molecules, these compounds can undergo various chemical transformations and have considerable synthetic potential. The main characteristic feature of diazo esters, which is common to all aliphatic diazo compounds, is that their reactions can proceed with either retention or elimination of the diazo fragment. The 1,3-dipolar cycloaddition of diazo esters to compounds containing multiple bonds is most typical of the first type of these transformations.[1,2] The second group of reactions proceeding with elimination of the nitrogen molecule are primarily characterized by generation of carbenes, their complexes with transition metals, cationoid reagents, and biradicals.[2—5] Subsequent transformations of these highly reactive intermediates are rather diversified and can be accompanied by the insertion of the $\rangle$C(R)COOAlk fragment into single bonds (in particular, into the C—H bond) and the addition at the multiple bonds (including aromatic bonds) to form three-membered rings, ylides and their transformation products, *etc*. One of the main ways of controlling the selectivity of reactions involving alkoxycarbonylcarbenes is to use catalytic dediazotization of diazo esters.

In the present study, we examined decomposition of methyl diazoacetate (MDA) in the presence of pyridine under thermal, photolytic, and thermocatalytic conditions and revealed the unusual formation of new methoxycarbonyl derivatives of pyrrole and 1,4,5,6-tetrahydropyridazine. These heterocyclic compounds are devoid of the pyridine fragment. However, the presence of pyridine in the reaction medium is essential for generation of these compounds from diazoacetate molecules. Thus, the slow addition of MDA to refluxing pyridine containing a catalytic amount of $Cu(acac)_2$ or $Rh_2(OAc)_4$ is accompanied by partial dediazotization of MDA to give a complex mixture of products from which two fractions were isolated by column chromatography on SiO_2. Each fraction was enriched with one of isomeric 1,4,5,6-tetrahydropyridazine-3,4,5,6-tetracarboxylic esters (**1**). Both isomers were isolated in individual form by repeated chromatography of the corresponding fractions. The total yields of esters **1** in the presence of $Cu(acac)_2$ or $Rh_2(OAc)_4$ were ~50 and 70%, respectively. In both cases, the ratio between the *trans*,*cis* and *cis*,*trans* isomers was ~1 : 1. Interestingly, we did not detect maleic and fumaric esters among the products of decomposition of MDA, which are generally pro-

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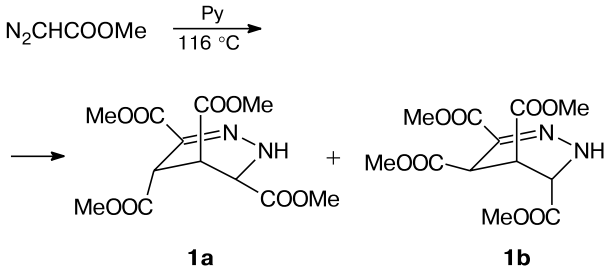
duced upon catalytic decomposition of diazo esters.[3] The reactions also did not give rise to trimethyl *trans*-aconitate, which is a product of formal trimerization of methoxycarbonylcarbene generated through dediazotization of MDA under the action of catalytic amounts of the $Cu(acac)_2 \cdot ZnCl_2 \cdot C_6H_5N$ complex.[6]

The structures of the resulting compounds were established by mass spectrometry and ^1H and ^{13}C NMR spectroscopy. In addition, the structure of isomer **1a** with the diaxial-equatorial arrangement of three methoxycarbonyl substituents at the C(4), C(5), and C(6) atoms was confirmed by X-ray diffraction analysis. The 2D-NOESY spectrum of this compound has cross-peaks corresponding to the through-space coupling of NH with H(6) as well as of H(5) with H(4) and H(6), whereas no clear coupling between the protons of the methoxy groups is observed. The position of the signal for the proton at C(6) was confirmed by the {C,H}-correlation experiment based on the fact that the ^{13}C NMR spectrum has signals for the C(4) and C(5) atoms at δ 37—39, whereas a signal for C(6) is observed at δ 52. We failed to crystallize isomer **1b**. However, the ^1H and ^{13}C NMR spectral patterns of this compound indicate that it has the structure of tetrasubstituted 1,4,5,6-tetrahydropyridazine, the NOESY and {C,H}-correlation experiments for **1b** also showing couplings of NH with H(6) and of H(5) with H(4) and H(6). However, unlike the spectrum of isomer **1a**, which has signals for the H(4) and H(6) protons at δ 4.4 and 4.2, respectively, the spectrum of **1b** is characterized by the reverse order of these signals (at δ 4.1 and 4.5 for H(4) and H(6), respectively). The vicinal spin-spin coupling constants in the spectra of both isomers are at most 4 Hz, which is indicative of the absence of axial-axial couplings. It can be assumed that isomerism of these compounds results from the different positions of the COOMe groups at the C(4) and C(6) atoms.



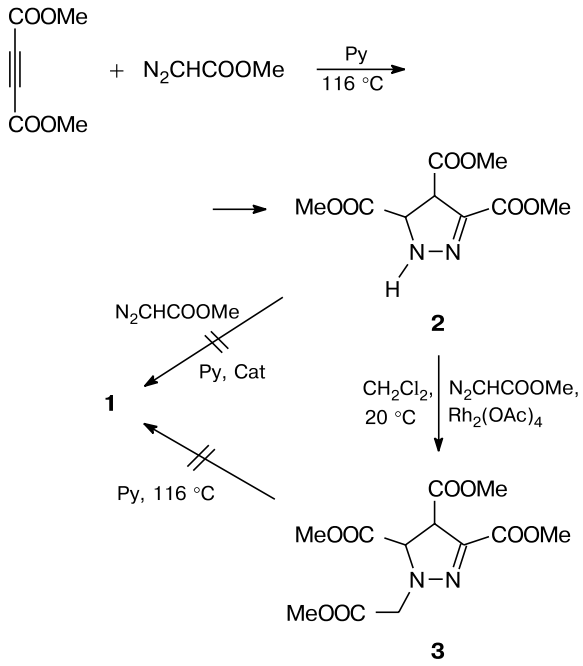
1a **1b**

In the absence of a catalyst, decomposition of MDA in refluxing pyridine proceeded very slowly. For example, the conversion of MDA achieved after 6—7 h was ~35%, the percentage of tetrahydropyridazines **1** (according to the ^1H NMR spectrum of the reaction mixture) being about 30%. However, a further increase in the reaction time did not virtually lead to an increase in the yield of the target product because of its thermal instability. After completion of decomposition of MDA (after ~20 h), compounds **1** were obtained in 30—33% yields.

It should be noted that pyridine plays a key role in the observed transformations of MDA. The use of triethylamine or dimethylaniline instead of pyridine did not lead to the formation of tetrahydropyridazines **1**. In the presence of quinoline (~120 °C), decomposition of MDA afforded isomeric tetraesters **1a,b** in 30—35% yields.

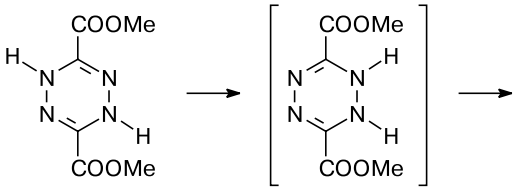
Direct photolysis of MDA in pyridine at 20 °C was also accompanied by its partial dediazotization to give tetrahydropyridazines **1**. However, their yields were at most 30%.

To reveal the possible paths of the formation of the tetrahydropyridazine structure in the course of the observed transformations, we studied catalytic decomposition of MDA in refluxing pyridine in the presence of half-molar amounts of dimethyl maleate, dimethyl fumarate, or 3,4,5-trimethoxycarbonyl-2-pyrazoline (**2**), which is a product of 1,3-dipolar cycloaddition of MDA to dimethyl fumarate. Because of the presence of the MDA fragments, these compounds could be precursors of tetrahydropyridazines **1**. However, it appeared that the first two reactions proceeded primarily as the usual 1,3-dipolar cycloaddition of MDA to the corresponding unsaturated compounds to give pyrazoline **2**, which did not react with MDA in pyridine both under the thermal and thermocatalytic (in the presence of $Rh_2(OAc)_4$) conditions. In the absence of pyridine (CH_2Cl_2, 20 °C), catalytic decomposition of MDA under the action of $Rh_2(OAc)_4$ led to the insertion of the carbene fragment into the N—H bond to form *N*-substituted pyrazoline **3**. Upon refluxing



in pyridine, compound **3**, like compound **2**, remained unchanged. Therefore, neither maleic and fumaric esters nor pyrazolines **2** and **3** are intermediates in the reactions giving rise to tetrahydropyridazines **1**.

Then we attempted to perform the reaction of dimethyl fumarate as a dienophile with heterocyclic compound **4** described earlier.[7] The latter compound is formally the cyclic dimer of MDA. Taking into account the compositions of the molecules and the character of bonds, both these compounds would be expected to be intermediates in the course of the transformation of MDA in pyridine, and their [4+2] cycloaddition followed by elimination of the N_2 molecule would be expected to afford tetrahydropyridazines **1**. However, according to the ^{1}H NMR spectroscopic data, both dimethyl fumarate and compound **4** remained unchanged upon refluxing in pyridine for 8 h, and tetrahydropyridazine **1** was not detected.



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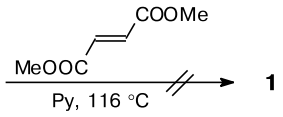
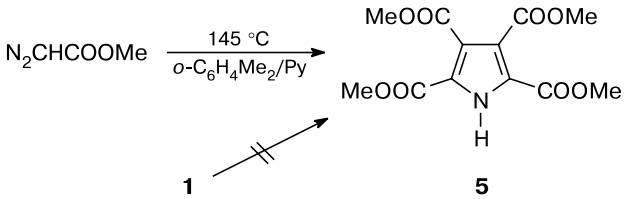


Consequently, compound **4** is not an intermediate of tetramerization and partial dediazotization of MDA in the presence of pyridine. In this connection, we assumed that tetrahydropyridazine derivatives can be formed through generation of pyridinium ylide and carbon-chain growth by the successive addition of the carbene fragments (CHCOOMe) and MDA. However, this hypothesis calls for further verification.

A decreases in the amount of pyridine used as the solvent to ~20 mol.% and the rise of the temperature by performing the reaction in refluxing *o*-xylene resulted in a change in the pathway of the transformations of MDA. Thermal decomposition of MDA (10 h) facilitated predominantly the reaction of methoxycarbonylcarbene that formed with *o*-xylene.[8] By contrast, the reaction performed under the thermocatalytic conditions ($Rh_2(OAc)_4$, 2 h) afforded a new compound, *viz.*, 2,3,4,5-tetramethoxycarbonylpyrrole (**5**), along with the adducts of CHCOOMe with xylene, which were detected by GLC-mass spectrometry. The yield of compound **5** reached 40%. It should be noted that this reaction did not give rise to six-membered heterocycle **1**. Product **5** was isolated by column chromatography on SiO_2 and its structure was confirmed both by spectroscopic data and X-ray diffraction analysis.



A special experiment showed that these reaction conditions (refluxing in *o*-xylene in the presence of pyridine) did not give rise to the transformation of tetrahydropyridazine **1** into pyrrole **5** with the formal elimination of the ammonia molecule. Hence, the formation of pyrrole **5** is even more unexpected than the formation of tetrahydropyridazine **1**, which retains for the most part the MDA fragments. However, it is not inconceivable that decomposition of MDA in this case also proceeds through the formation of pyridinium ylides and a particular common intermediate. Under more drastic conditions and at a low concentration of pyridine, aromatization of the latter intermediate giving the pyrrole derivative in one of the last steps becomes a preferred process. The elucidation of the characteristic features of these reactions and the mechanism of formation of heterocycles **1** and **5** will be the subject of our further investigation.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-200 (200.13 and 50.3 MHz) and Bruker DRX-500 (500.13 MHz) spectrometers in solutions in $CDCl_3$ containing 0.05% of Me_4Si as the internal standard. The mass spectra were measured on a Finnigan MAT INCOS-50 instrument (EI, 70 eV). The reactions were carried out with the use of freshly distilled pyridine. The catalysts $Rh_2(OAc)_4$ and $Cu(acac)_2$ were purchased from Acros Organics. 3,4,5-Trimethoxycarbonyl-2-pyrazoline (**2**)[9] and dihydro-3,6-bismethoxycarbonyl-1,2,4,5-tetrazine (**4**)[7] were prepared according to known procedures. Column chromatography was carried out with the use of silica gel 60 (0.063—0.200 mm; Merck).

Single-crystal X-ray diffraction study of compounds **1a** and **5** was carried out on an automated Bruker 1K SMART CCD diffractometer (Mo-Kα radiation). The crystals are monoclinic, at 293 K a = 10.379(3) Å, b = 14.408(5) Å, c = 9.772(4) Å, V = 1455.3(8) Å^3, Z = 4, d_{calc} = 1.443 g cm^{-3}, space group $P2(1)/c$ for compound **1a** and a = 17.428(4) Å, b = 10.358(2) Å, c = 8.013(2) Å, V = 1319.0(5) Å^3, Z = 4, d_{calc} = 1.507 g cm^{-3}, space group $C2/c$ for compound **5**. All calculations were carried out with the use of the SHELXTL PLUS program package.[10] The atomic coordinates and complete data for compounds **1a** and **5** were deposited with the Cambridge Structural Database. The selected geometric parameters of the compounds are given in Tables 1 and 2.

3,4,5,6-Tetra(methoxycarbonyl)-1,4,5,6-tetrahydropyridazine (1). ***Method A.*** A solution of methyl diazoacetate (MDA)

Table 1. Selected geometric parameters of molecule **1a**

Bond	*d*/Å	Angle	ω/deg
N(1)—N(2)	1.338(2)	N(2)—N(1)—C(6)	121.2(2)
N(1)—C(6)	1.442(3)	N(1)—N(2)—C(3)	119.1(2)
N(2)—C(3)	1.289(2)	N(2)—C(3)—C(4)	125.5(2)
C(3)—C(4)	1.504(3)	C(3)—C(4)—C(5)	110.6(2)
C(4)—C(5)	1.534(3)	C(4)—C(5)—C(6)	107.5(2)
C(5)—C(6)	1.539(3)	C(5)—C(6)—N(1)	107.9(2)

Table 2. Selected geometric parameters of molecule **5**

Bond	*d*/Å	Angle	ω/deg
N(1)—C(2)	1.359(2)	C(2)—N(1)—C(5)	109.9(2)
C(2)—C(3)	1.388(2)	N(1)—C(2)—C(3)	107.9(2)
C(3)—C(4)	1.407(3)	C(2)—C(3)—C(4)	107.1(1)
C(2)—C(O)	1.475(2)	N(1)—C(2)—C(O)	123.3(1)
C(3)—C(O)	1.485(2)	C(2)—C(3)—C(O)	127.1(1)

(5.0 g, 50 mmol) in pyridine (40 mL) was added with stirring and refluxing to a solution of $Rh_2(OAc)_4$ (0.11 g, 0.25 mmol) in pyridine (80 mL) during 2 h. The reaction mixture was refluxed with stirring for 30 min and the pyridine was removed *in vacuo*. The black resinous precipitate that formed was dissolved in a minimum volume of AcOEt and passed through a layer of silica gel (~8 cm); elution was performed with AcOEt (20 mL). The solvent was removed *in vacuo* and the residue was chromatographed on a column with SiO_2 (benzene—AcOEt, 1 : 1, as the eluent). Fraction of approximately the same mass were obtained. The fractions were enriched with isomers **1a** and **1b**, respectively, by 80—85%; the total yield was 2.68 g (68%). The isomers were separated by repeated chromatography of each fraction.

Compound 1a, weakly colored crystals, m.p. 149—150 °C. ^{1}H NMR ($CDCl_3$), δ: 3.68, 3.76, 3.84, and 3.85 (all s, 4 3 H each, OMe); 3.74 (dd, 1 H, H(5), $J_{4,5}$ = 1.8 Hz, $J_{5,6}$ = 3.6 Hz); 4.12 (dt, 1 H, H(6), $J_{5,6}$ = 3.6 Hz, $J_{1,6} = J_{4,6}$ = 1.8 Hz); 4.36 (t, 1 H, H(4), $J_{4,5} = J_{4,6}$ = 1.8 Hz); 7.21 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 37.8 (C(5)); 39.4 (C(4)); 51.5 (C(6)); 52.3, 52.8, 52.9, and 53.0 (4 OMe); 126.3 (C(3)); 164.5, 168.6, 168.9, and 170.9 (4 CO). Partial MS, *m*/*z* (I_{rel} (%)): 316 (6) $[M]^+$, 284 (12), 257 (8), 225 (24), 197 (100). Selected geometric parameters of molecule **1a** are given in Table 1.

Compound 1b (with an impurity of ~6% of isomer **1a**), viscous weakly colored liquid. ^{1}H NMR ($CDCl_3$), δ: 3.69, 3.72, 3.76, and 3.83 (all s, 4 3 H each, OMe); 3.86 (dd, 1 H, H(5), $J_{4,5}$ = 2.6 Hz, $J_{5,6}$ = 1.3 Hz); 4.18 (dd, 1 H, H(4), $J_{4,5}$ = 2.6 Hz, $J_{4,6}$ = 1.7 Hz); 4.50 (ddd, 1 H, H(6), $J_{1,6}$ = 3.1 Hz, $J_{4,6}$ = 1.7 Hz, $J_{5,6}$ = 1.3 Hz); 7.18 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 37.3 (C(4)); 38.7 (C(5)); 52.3, 52.8, 53.0, and 53.2 (4 OMe); 52.9 (C(6)); 128.1 (C(3)); 164.5, 169.5, 170.2, and 170.4 (4 CO). Partial MS, *m*/*z* (I_{rel} (%)): 316 (7) $[M]^+$, 284 (12), 257 (15), 225 (25), 197 (100). Found (%): C, 45.25; H, 5.49; N, 8,47. $C_{12}H_{16}N_2O_8$. Calculated (%): C, 45.57; H, 5.10; N, 8,86.

Method B. A mixture of tetrahydropyridazines **1a** and **1b** was prepared analogously from MDA (2.0 g, 20 mmol) and $Cu(acac)_2$ (0.10 g, 0.38 mmol) in refluxing pyridine (20 mL) in a yield of 0.79 g (50%) in a ratio of ~1 : 1.

Method C. A solution of MDA (0.2 g) in pyridine (2 mL) was irradiated using a quartz lamp for 8 h, the solvent was removed *in vacuo*, and the residue was analyzed by ^{1}H NMR spectroscopy. The total yield of isomers **1a** and **1b** was ~30%, the isomer ratio was ~1 : 1.

Method D. A solution of MDA (0.2 g) in pyridine (2 mL) was refluxed for 20 h, the solvent was removed *in vacuo*, and the residue was analyzed by ^{1}H NMR spectroscopy. The total yield of isomers **1a** and **1b** was 30—33%, the isomer ratio was ~1 : 1.

3,4,5-Tri(methoxycarbonyl)-1-(methoxycarbonylmethyl)-2-pyrazoline (3). Methyl diazoacetate (0.33 g, 3.3 mmol) was added to a solution of 3,4,5-tri(methoxycarbonyl)-2-pyrazoline (**2**) (0.73 g, 3 mmol) and $Rh_2(OAc)_4$ (7.5 mg, 0.017 mmol) in CH_2Cl_2 (4 mL) at 20 °C for 2 h. Then the reaction mixture was stirred for 30 min and the solvent was removed *in vacuo*. The residue was chromatographed on a column with SiO_2 to obtain a fraction (0.61 g). According to the ^{1}H NMR spectroscopic data, this fraction contained ~85% of pyrazoline **3** (58% yield), 10% of the starting pyrazoline **2**, and 5% of dimethyl fumarate. ^{1}H NMR of compound **3** (200 MHz, $CDCl_3$), δ: 3.72, 3.77, 3.78, and 3.81 (all s, 3 H each, OMe); 4.29 and 4.46 (both d, 1 H each, CH_2, ^2J = 18.2 Hz); 4.49 (d, 1 H, H(4), $J_{4,5}$ = 10.0 Hz); 4.92 (d, 1 H, H(5), $J_{4,5}$ = 10.0 Hz). The sample thus obtained was refluxed in pyridine for 7 h. Then the pyridine was completely removed *in vacuo*. According to the ^{1}H NMR spectrum of the residue, the composition of the reaction mixture remained unchanged and the formation of tetrahydropyridazine **1** was not observed.

2,3,4,5-Tetra(methoxycarbonyl)pyrrole (5). A solution of MDA (1.0 g, 10 mmol) in *o*-xylene (4 mL) was added with stirring and refluxing to a solution of $Rh_2(OAc)_4$ (22 mg, 0.05 mmol) in a mixture of *o*-xylene (8 mL) and pyridine (0.16 g, 2 mmol) for 2.5 h. The reaction mixture was refluxed with stirring for 30 min and the solvents were removed *in vacuo*. The black oily residue was supported onto silica gel (~8 mL) and eluted first with benzene (100 mL) to remove the adducts of methoxycarbonylcarbene with *o*-xylene[8] and then with ethyl acetate (100 mL). A solution in AcOEt was concentrated *in vacuo* and the resulting red oil was purified by column chromatography (SiO_2, benzene—AcOEt, 1 : 1, as the eluent). Pyrrole **5** was obtained in a yield of 0.28 g (38%) as colorless crystals, m.p. 127—128 °C, R_f = 0.6. ^{1}H NMR ($CDCl_3$), δ: 3.88 and 3.91 (both s, 6 H each, 4 OMe); 10.4 (br. s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 52.6 and 52.8 (2 OMe each); 121.6 (C(3) and C(4)); 123.4 (C(2) and C(5)); 159.2 and 163.3 (2 CO each). Partial MS, *m*/*z* (I_{rel} (%)): 299 (53) $[M]^+$, 268 (67), 236 (100). Found (%): C, 47.91; H, 4.49; N, 4.51. $C_{12}H_{13}NO_8$. Calculated (%): C, 48.17; H, 4.38; N, 4.68. Selected geometric parameters of molecule **5** determined by X-ray diffraction analysis are given in Table 2.

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